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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/103,846	06/24/1998	RICHARD P. WOYCHIK	CASE-03330	3529

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EXAMINER
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ART UNIT	PAPER NUMBER
1632	29

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Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary

Application No.	Applicant(s)
09/103,846	Woychik, R. et al.
Examiner	**Art Unit**
Joseph Woitach	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 17, 2003* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *37, 39-46, and 48-57* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *37, 39, 40, 42-46, and 48-57* is/are rejected.

7) ☒ Claim(s) *41* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This is an original application filed June 24, 1998.

Applicants' amendment filed April 17, 2003, paper number 28, has been received and entered. Claims 1-8, 10-12, 14-22, 24-26, 28, 35 and 36 have been canceled. Claims 38 and 47 have been canceled. Claims 37, 39, 40 and 46 have been amended. Claims 51-57 have been added. Claims 37, 39-46, 48-57 are pending and currently under examination.

Claim Objections

Claim 51 is objected to because of the following informalities: the claim appears to be a modified version of claim 37, however newly added claim 51 contains editor marks with recitations of embodiments which are also presented previously in the claim (70% limitation). Newly added claims should not contain or indicate modifications to the claim. Claim 51 should be amended to delete the portion of the claim between the brackets.

Appropriate correction is required.

Specification

The disclosure stands objected to because the specification contains several references to an active executable code.

Applicants cite the actual text and argue that the teachings are not an improper incorporation by reference. See Applicants' amendment, peas 6-7, Section 1.

Examiner agrees with Applicants arguments, however the specification can not contain an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. Amending the specification to make the hyperlink a non-executable code would obviate the objection.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 37, 39-46, 48-50 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn.

The amendment to the claims has obviated each of the specific basis of rejection.

Newly added claims 51-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Newly added claim 51 is unclear in the recitation of "[,wherein said treating is under....stem cells is produced]" in step (c). It is unclear if this recitation is in reference to a second treatment or if it simply reiterates the conditions and limitation set forth in step (b)(i). Dependent claims are included in the rejection because they fail to further clarify the basis of the rejection and only recite greater percentages or particular gene of interest.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 37, 39, 40, 42, 43, 46, 48 and 49 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Schafer *et al.*

Applicants re-iterate the newly amended method steps of claim 37, and note that for an obviousness rejection all the elements encompassed by the claims must be taught in the cited

reference. Applicants point out specifically that Shafer *et al.* teach that "one mutation in every 1000 genes" is indicated and that "a large number of mutations per individual is undesirable..." and argue that guidance of Shafer *et al.* teach away from the claimed invention. See Applicants' amendment, pages 8-9, Section 3A. Applicants' arguments have been fully considered, but not found persuasive.

The portions of the specification of Shafer *et al.* cited by Applicants are noted, however Shafer *et al.* clearly teach that heterozygous mutations are introduced into a gene of interest. The present claims encompass using conditions which produce mutations in 70% of the genes of the genome, however Shafer *et al.* clearly teach that the methods of introducing mutations should represent "mutations across the entire genome" and that the methods should result in a "diverse range of mutations". Finally, Shafer *et al.* teach that "for any given gene there should be more than one mutation-carrying individual" (column 4, lines 45-54). The instant claims encompass practicing the method in any number of starting cells and do not limit the conditions wherein 70% of the genes of a single cell contain a mutation. Clearly Shafer *et al.* teach that a diverse range of mutations should be introduced into the whole (100%) of the genome. The fact that methods taught by Shafer *et al.* teach reasons for practicing the methods with a large number of starting cells to reduce the total number of mutations per cell in order to represent alterations throughout the entire genome does not teach away from the instantly claimed invention because the pending claims encompass this method. It is noted that Shafer *et al.* does not specifically recite or provide the conditions for 70%, but does not teach away from the claimed methods

because clearly Shafer *et al.* teach that 100% of the genome should be affected by the methods and represented by the resulting cells. The present claims encompass practicing the methods in any number of starting cells as long as the final population represent alterations in at least 70% of the genes of the genome. Since the methods of Shafer *et al.* teach that 100% of genome should be altered by the mutating conditions, it is maintained that Shafer *et al.* does teach all the limitations encompassed by the claims.

Therefore, for the reasons above and of record, the rejection is maintained.

Claims 37, 39, 40, 43, 45-47 and 49 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Goodfellow *et al.*

Applicants note the amendments to the claims to encompass that "it is at least 70% probable that at least one modification in substantially every gene" is produced and argue that Goodfellow *et al.* do to teach this limitation, in particular in a small collection of cells. See Applicants' amendment, page 9, Section 3B. Applicants' arguments have been fully considered, but not found persuasive.

Initially, Examiner agrees that Goodfellow *et al.* does not teach to use a small number of starting cells such as encompassed by claim 41, however does teach that a series of mutations in a gene of interest can be obtained in as little as 1000 mice (column 12, lines 26-54). Further, the method conditions contemplated by Goodfellow *et al.* should result in the mutation rate of 1/500 in a gene of interest, which requires that many more alteration are introduced throughout the

genome in the practice of the method. The conditions taught by Goodfellow *et al.* thus encompass using a relatively small number of starting cells for a single gene relative to the 50-100,000 genes proposed to exist (column 7, lines 37-40). With regard to specifically teaching conditions for 70% of the genes having a mutation, as argued above with respect to Schafer *et al.*, Goodfellow *et al.* does not specifically teach to use conditions which result in alterations in at least 70% of the genes of the genome. However, Goodfellow *et al.* clearly teach that any gene of interest can be targeted and contemplate the total number of genes present in a given genome. Since any gene can be a gene of interest, the methods contemplated by Goodfellow *et al.* necessarily require that every gene be altered in the conceptual practice of the method. Furthermore, while the specific conditions taught by Goodfellow *et al.* focus on obtaining alterations in a single gene of interest, providing multiple series of mutations in a single gene would require alterations throughout the entire genome. Similar to the teaching of Shafer *et al.* clearly Goodfellow *et al.* teach that a diverse range of mutations should be introduced into the whole (100%) of the genome. Again it is noted that Goodfellow *et al.* does not specifically recite or provide the conditions for 70%, and that the rate of mutation per cell is less than 70% mutation/gene but does not teach away from the claimed methods because clearly Goodfellow *et al.* teach that any gene of interest, thus 100% of the genes of the genome are subject and can be affected by the methods. The present claims encompass practicing the methods in any number of starting cells as long as the final population represent alterations in at least 70% of the genes of the genome. Since the methods of Goodfellow *et al.* teach that any gene of interest is the target

of the methods 100% of genome should be altered by the methods, it is maintained that Goodfellow *et al.* does teach all the limitations encompassed by the claims.

Therefore, for the reasons above and of record, the rejection is maintained.

Claims 37, 39, 40 and 42-50 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Schafer *et al.*, Goodfellow *et al.* in view of either Kohler *et al.* (IDS reference JNCI, 1993) or Guay-Woodford *et al.* (IDS reference J. Int. Soc. Neph., 1996).

The traverse for the teaching of Schafer *et al.* and Goodfellow *et al.* are summarized above. Briefly, it is argued that neither Schafer *et al.* nor Goodfellow *et al.* teach each of the limitations required by the amended claims and teach away from the claimed invention because a small number of cells are not used to practice the method as claimed. With respect to the teaching of Kohler *et al.* and Guay-Woodford *et al.* Applicants do not argue or discuss the specific teachings. Instead Applicants argue that the case law relied upon was misunderstood (Section 3C(i)), and more recent case law raises the bar to prevent hindsight reasoning citing *In re Rouffet et al.* Further, it is argued that the reliance on *Nilssen* is misplaced and that the Examiner must provide evidence for combining the teaching in each of the cited references. See Applicants' amendment, pages 9-12, Section 3C. Applicants' arguments have been fully considered, but not found persuasive.

As argued above, it is maintained that the teaching of Schafer *et al.* and Goodfellow *et al.* do not teach away, rather the methods taught by both Schafer *et al.* and Goodfellow *et al.* are

encompassed by the claims as amended. With respect to combining methods of generating mutations and methods of detecting mutations, as indicated in the previous office action both Schafer *et al.* and Goodfellow *et al.* teach that methods of detecting the specific mutation in the gene of interest would be required. One of skill in the art would be motivated to use methods of detection because this is what is taught by Schafer *et al.* and Goodfellow *et al.* Further, with respect to the teaching of Kohler *et al.* and Guay-Woodford *et al.*, beyond the demonstration that the specific genes and mutations found in these genes represent one of the many genes in the genome, the reasons for analyzing these genes is that they are associated with cancer. Furthermore, mutations in these genes result in phenotypically observable changes which is also supported by the teaching of Schafer *et al.* and Goodfellow *et al.* The motivation to combine the teaching of Schafer *et al.* and Goodfellow *et al.* to observe changes in the specific genes taught by teaching of Kohler *et al.* and Guay-Woodford *et al.* is more than just desirable as argued by Applicants. The Kohler *et al.* and Guay-Woodford *et al.* provide clear motivation to study mutations in the genes associated with cancer. As indicated in the previous office action, one having ordinary skill in the art would have been motivated to pick p53 and PKD genes as genes of interest because of their implicated roles in human diseases and because of the need for further characterization in these diseases. In view of the teachings of each Kohler *et al.*, Guay-Woodford *et al.*, Schafer *et al.* and Goodfellow *et al.* as a whole there would have been a reasonable expectation of success to target p53 and PKD as genes of interest given the successful results of Schafer *et al.* and Goodfellow *et al.* for several other genes of interest, and the

teachings of both Kohler *et al.* and Guay-Woodford *et al.* that specific mutations can be made and already exist and result in detectable phenotypic changes.

Thus, for the reasons above and of record, the claimed invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claim is allowed. Claims 41 and newly added claims 51-57 are free of the art of record because the art fails to teach that as little as 200-600 ES cells could successfully be used in the recited methods. As indicated in the previous office action, the closest teaching to this low range of cells as a starting material is by Schafer *et al.* who suggest that as few as 1000 organisms (i.e cells) could be used to obtain a single mutant copy of a gene (column 6; lines 45-54). In addition, Schafer *et al.* do teach as little as 300 mice can be used (Example 1: column 14; lines 58-67), however in this example the spermatogonia are the target cells, and thus, represent many more cells as starting material than 300 cells, and therefore would be outside the range of 200-600 cells.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Joseph T. Woitach

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP 1800/1630